Informational Update:

Kaletra® Oral Solution Toxicity in Neonates—Lopinavir, Ethanol and/or Propylene Glycol?

Pediatric Advisory Committee Meeting
September 23, 2011

Debra Boxwell, PharmD
Division of Pharmacovigilance (DPV) II
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)
Food and Drug Administration

Outline

- Background Information
- Ingredient Toxicities
- AERS Cases
- Pharmacokinetics
- Summary

Kaletra®

- Protease inhibitor
- Indication: Treatment of HIV-1 infection in combination with other antiretroviral agents
- Tablets and oral solution approved in 2000 for adults and children 6 months of age and older
- Oral solution approved in June 2008 for use in children 14 days of age and older

Revisiting Kaletra

- Brought before the PAC in December 2009
- Findings included 8 cases of cardiac abnormalities:
  - 3 sets of premature newborn twins: bradycardia, dilated cardiomyopathy
  - 12 month old: CHF secondary to anemia and pneumonia after rx with traditional medicine by spiritual healer
  - 13 yo: acute paroxysmal tachycardia with Kivexa (abacavir/lamivudine) and Kaletra. Event not thought to be due to antiretroviral therapy
- Conclusion: Reports of cardiac abnormalities consistent with labeling, which includes PR and QT interval prolongation in Warnings and Precautions, and bradyarrhythmias in Postmarketing Experience

Ingredients

- Kaletra® oral solution (80 mg lopinavir/ 20 mg ritonavir per mL)
- Ethanol (42.4% v/v or 356 mg/mL)
- Propylene glycol (15.3% w/v or 152.7 mg/mL)
  - For solubility; no good alternatives

v/v=volume to volume; w/v=weight per volume

Propylene Glycol and HIV Drugs

- Amprenavir—55% w/v (discontinued 2005)
- Lopinavir/ritonavir—15.3% w/v
- Fosamprenavir—1% w/w

- Lamivudine
- Abacavir
- Ritonavir

Ongoing Monitoring

- 3 sets of twins developed bradycardia and/or congestive cardiomyopathy after receiving Kaletra oral solution

- Three sets of twins (n=6):
  - All had cardiotoxicity
  - All born prematurely
  - 3 of 6 had acute renal failure

Light bulb Moment!

- A physician from France thought the adverse events may be due to either lopinavir or propylene glycol

- Renal failure is a known toxicity associated with propylene glycol
- Could these toxicities be due to an excipient?

Labeled Lopinavir/ritonavir Adverse Events

- PR and QT interval prolongation:
  - 1st, 2nd, 3rd-degree AV block
  - Torsades de pointes

- In a pharmacokinetic and safety study in infants (n=31; age: 14 days-6 months):
  - Moderate to severe AEs: decreased neutrophil count (n=3), anemia (n=2), high potassium (n=2), and low sodium (n=2)

Acute Ethanol Toxicity

- Coma, hypoglycemia, and hypothermia—classic signs of ethanol intoxication in young children

- Seizures, often due to hypoglycemia in children
- Hypotonia
- Hyporeflexia
- Gastritis, gastrointestinal bleeding
- Hypokalemia
- Respiratory depression and failure

- Serious cases: acute hepatitis, acute pancreatitis, rhabdomyolysis, cardiovascular toxicity

Propylene Glycol Toxicity

- Cardiovascular
  - Hypotension, bradycardia, widening of the QRS interval (with rapid IV infusion)
- Central Nervous System
  - CNS depressant effects are similar to those of ethanol
  - Considered to be approximately one-third as intoxicating as ethanol
  - Associated with seizures
- Acidosis
  - Lactic acidosis (metabolized to lactic acid by the liver)
  - Usually mild, with serum lactate levels ranging from 2 to 6 mEq/L

Propylene Glycol Toxicity

- Nephrotoxicity
  - Multiple case reports of renal toxicity associated with propylene glycol in the literature
  - In many cases, hyperosmolality was also documented
  - Association between serum propylene glycol concentrations and osmol gap

AERS Searches

(from preapproval to 2 Sept 2010)

- 2 Searches:
  - All Kaletra reports in children 0-2 years of age
  - Adverse events associated with lopinavir, propylene glycol, and/or ethanol:
    - Rate and Rhythm Disorders
    - Renal Failure and Impairment
    - Metabolic Acidosis (excluding diabetic acidosis)
    - Hyperosmolar State
    - Seizures and Seizure disorders
    - Cardiomyopathies

AERS Search Results

- A total of 344 reports were individually examined
- Transplancental exposure were excluded
- 17 reports, representing 10 unduplicated cases
- All 10 cases were in neonates
- 8 were born prematurely

Table 1: Key Characteristics of AERS Cases (n=10)

Gestational Age at Birth in Preterm Infants (n=8)	28 to 34 6/7 weeks
Weight of Premature Infants (n=6)	Mean: 1512 g (range, 990-2200 g)
Outcome	Death: 1, Survived 9
Age First Received LPV/r	Day of birth: 7, Day after birth: 1, Day 34: 1, Unknown: 1
Reported LPV/r Dose *[Children 14 days to 6 months: 300/75 mg/m^2 (lopinavir/ritonavir) or 16/4 mg/kg twice a day]	Recommended dose for older infants*: 7 Overdose: 2 Acute—1 Chronic—1 Unknown: 1
Onset of First Adverse Event	Within 6 days: 8, Day 20: 1, Unknown: 1
Evidence of Recovery or Improvement after LPV/r Discontinued (n=9)	Within 5 days: 6 Unknown: 3

Toxicities Seen in the 10 Cases

(may have >1 event)

- Cardiac toxicity (n=7): bradycardia, complete AV block, congestive cardiomyopathy, cardiac failure, and cardiogenic shock
- Elevated lactate (n=2), plus 1 in high-normal range
- CNS toxicity (n=3): asthenia, somnolence, abnormal EEG, altered state of consciousness, hypotonia
- Acute renal failure (n=5), plus increased serum creatinine in 1; hyperkalemia in 4

Toxicities (con't)

- Respiratory complications (n=3): dyspnea and wheezing, respiratory failure, neonatal respiratory arrest

- Gastrointestinal adverse events (n=5): vomiting, failure to thrive, abdominal distention

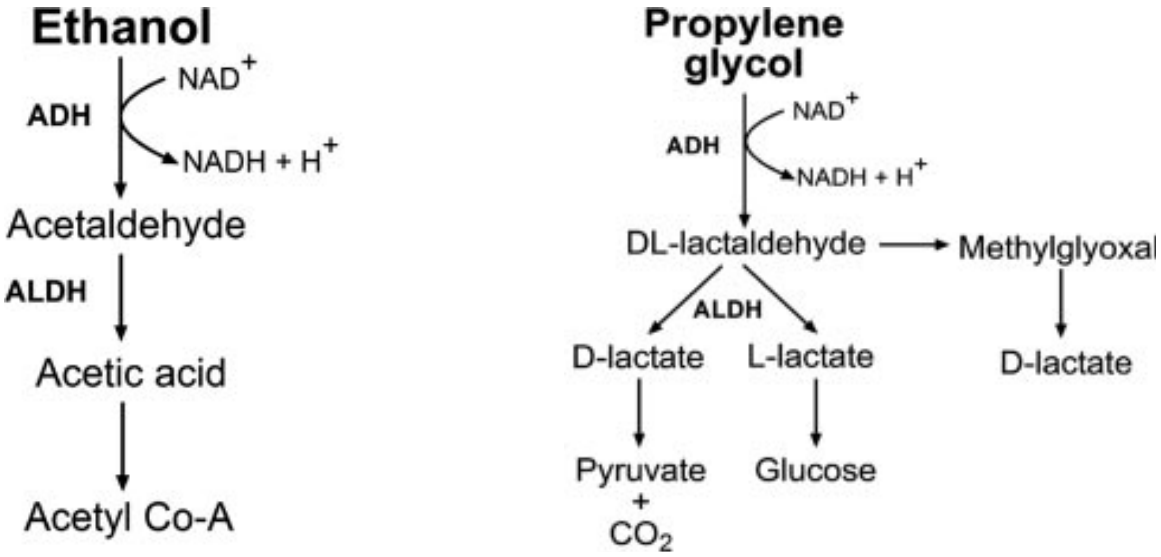
- Hematologic abnormalities (n=3): anemia or a decreased hemoglobin count in 3, and increased reticulocyte count in 1

Death Due to Med Error (2007)

- Born at 30 2/7 weeks gestation; 1.4 kg
- Received her only dose at 34 days of age (postmenstrual age of 35 1/7 weeks; 2.2 kg)
- Intended dose was 0.65 mL (52 mg), but due to a medication error, she was given 6.5 mL (520 mg) or 10 times the intended dose

- Dear Healthcare Professional Letter
- Labeling update: caution with dosing of oral solution

Key Pharmacokinetic Points



Both are alcohols with similar pharmacokinetic properties

Ethanol: 95% in the liver by alcohol dehydrogenase (ADH) to acetaldehyde

Propylene glycol: 55-75% metabolized by ADH to DL-lactaldehyde

Key Pharmacokinetic Points

- Ethanol has a 10 to 20 times greater affinity for ADH than other alcohols
- Ethanol competitively inhibits the metabolism of propylene glycol when administered together, delaying propylene glycol elimination

Pharmacokinetics in Neonates

- Propylene glycol half-life in premature infants: 19 hours* (oral solution dosed BID)
- Neonates have immature hepatic and renal function

*Glasgow AM, Boeckx, RL, Miller MK, MacDonald MG, August GP. Hyperosmolality in small infants due to propylene glycol. Pediatrics 1983;72(3):353-5.

Measured Lopinavir Levels

- Lopinavir crosses the placenta, with cord blood concentrations averaging 16.7% (range, 5-25%) of the maternal plasma concentrations

- 6 of the mothers were documented to have been taking LPV/r at the time they gave birth
  - 5 of their neonates received LPV/r oral solution on the day of birth

- In a pharmacokinetics study, the mean steady-state Cmax for lopinavir was 5.2 ± 1.8 µg/mL in full-term infants approximately 6 weeks of age

Table 2: Neonatal Exposure to Lopinavir, Ethanol, and Propylene Glycol

Case #	Gestational Age at Birth Body Weight	Reported LPV/r Dose	Highest Measured Lopinavir Level (µg/mL)	Calculated Blood Ethanol Concentration per Dose (mg/dL)	Daily Propylene Glycol Intake (mg/kg/day)
1	28 weeks 990 g	230 mg/m^2 BID	--	11.0	89.5
2	28 weeks 1083 g	230 mg/m^2 BID	--	10.6	87.4
5	34 6/7 weeks 2.1 kg	30 mg TID	25.3	6.8	81.8
6	34 6/7 weeks 2.2 kg	30 mg TID	20.2	6.5	78.1
7	30 2/7 weeks 1.4 kg	520 mg x 1	28.5	111	451.2 x 1
9	28 1/7 weeks 1.3 kg	40 mg BID	16.2	14.5	117.5
10	Unknown 3.19 kg	20 mg/kg BID	29.2	11.3	76.4

Exposure of Alcohols

- Ethanol and propylene glycol levels were not measured in any of the AERS cases
- HOWEVER—body weight and length, and dosing was available for 7 of the 10 patients, allowing for calculations
- Examine exposure of each product

Blood Ethanol Levels in Children

- 1984: American Academy of Pediatrics (AAP)--blood ethanol concentration (BEC) should not exceed 25 mg/dL following a single dose of an alcohol-containing medication

- 2010 reflection paper: European Medicines Agency (EMA)--BEC not exceed 12.5 mg/dL following a single dose based on the impairment of psychomotor skills

Calculated Blood-Ethanol Estimations

- Blood ethanol concentration (BEC) calculation (mg/dL):

$$\frac{\text{Volume Ingested (mL)} \times \text{\% EtOH (0.424)} \times \text{Specific Gravity (0.80 g/mL)}}{\text{Volume of Distribution} \times \text{Body Weight (kg)}}$$

- Volumes of distribution:
  - Adults (0.6 L/kg)
  - Full-term neonates (0.75 L/kg)
  - Premature neonates (0.9 L/kg)

- EMA: 12.5 mg/dL not be exceeded following a single dose

Table 3: Neonatal Exposure to Lopinavir, Ethanol, and Propylene Glycol

Case #	Gestational Age at Birth Body Weight	Reported LPV/r Dose	Highest Measured Lopinavir Level (µg/mL)	Calculated Blood Ethanol Estimation per Dose (mg/dL)	Daily Propylene Glycol Intake (mg/kg/day)
1	28 weeks 990 g	230 mg/m^2 BID	--	11.0	89.5
2	28 weeks 1083 g	230 mg/m^2 BID	--	10.6	87.4
5	34 6/7 weeks 2.1 kg	30 mg TID	25.3	6.8	81.8
6	34 6/7 weeks 2.2 kg	30 mg TID	20.2	6.5	78.1
7	30 2/7 weeks 1.4 kg	520 mg x 1	28.5	111	451.2 x 1
9	28 1/7 weeks 1.3 kg	40 mg BID	16.2	14.5	117.5
10	Unknown 3.19 kg	20 mg/kg BID	29.2	11.3	76.4

Calculated Blood-Ethanol Estimations

- Case report: Ethanol elimination rate in premature twins (1.1 kg and 1.9 kg) was 8 mg/dL and 7 mg/dL per hour, respectively*
- Even at reduced elimination rate, accumulation of ethanol most likely will not occur

*Seppälä M, Räihä NCR, Tamminen V. Ethanol elimination in a mother and her premature twins. Lancet 1971;1(7710):1188-9.

Propylene Glycol

- A solvent and vehicle for intravenous, topical, and oral medications that are insufficiently soluble or unstable in water:
  - Oral—Agenerase (amprenavir)
  - Topical—Silvadene
  - Intravenous—Phenytoin, lorazepam

- Also used in:
  - Processed foods
  - Animal food as a carbohydrate substitute
  - Cosmetics, toothpaste, shampoo, mouth wash, deodorant
  - Antifreeze (major ingredient)
  - Hydraulic fluid products (major ingredient)

Propylene Glycol

- In 1974, World Health Organization (WHO) set 25 mg/kg as maximum acceptable daily intake when used as a food additive (based on metabolic and toxicological data)

- In 1982, FDA classified propylene glycol as a compound that is “generally regarded as safe (GRAS)”

Calculated Propylene Glycol Ingestion

- Ingestion based on body weight: mg/kg/day
- WHO: Up to 25 mg/kg/day

Table 4: Neonatal Exposure to Lopinavir, Ethanol, and Propylene Glycol

Case #	Gestational Age at Birth Body Weight	Reported LPV/r Dose	Highest Measured Lopinavir Level (µg/mL)	Calculated Blood Ethanol Concentration per Dose (mg/dL)	Daily Propylene Glycol Intake (mg/kg/day)
1	28 weeks 990 g	230 mg/m^2 BID	--	11.0	89.5
2	28 weeks 1083 g	230 mg/m^2 BID	--	10.6	87.4
5	34 6/7 weeks 2.1 kg	30 mg TID	25.3	6.8	81.8
6	34 6/7 weeks 2.2 kg	30 mg TID	20.2	6.5	78.1
7	30 2/7 weeks 1.4 kg	520 mg x 1	28.5	111	451.2
9	28 1/7 weeks 1.3 kg	40 mg BID	16.2	14.5	117.5
10	Unknown 3.19 kg	20 mg/kg BID	29.2	11.3	76.4

Calculated Propylene Glycol Ingestion

- Calculated intake does NOT factor in:
  - Delayed elimination (ethanol having a greater affinity and competing for ADH)
  - Prolonged half-life in premature neonates (19 hours)

Discussion—Lopinavir, Ethanol and/or Propylene Glycol?

- Cardiac toxicity: LPV/r, Ethanol (high dose)
- Acidosis: Propylene glycol, Ethanol, LPV/r
  - ↓
- Hyperkalemia
  - ↓
  - (range, 6.4-9.4; n=4)
- Cardiac toxicity

Discussion—Lopinavir, Ethanol and/or Propylene Glycol?

- Renal failure: Propylene glycol,
  LPV/r (CrCl <50 mL/min in 2-3% clinical trials)
- Hematologic (anemia and inc reticulocyte count): LPV/r, Ethanol, and Propylene glycol

Discussion—Lopinavir, Ethanol and/or Propylene Glycol?

- CNS: Ethanol and Propylene glycol
- Respiratory: Ethanol and Propylene glycol
- Gastrointestinal: Ethanol and Propylene glycol, LPV/r

New Labeling in February 2011

- Dosage and Administration
  - Pediatric Patients
    - KALETRA oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days have been attained *[see Warnings and Precautions (5.2)]*.

New Labeling in February 2011

- **Warnings and Precautions**
  - **5.2 Toxicity in Preterm Neonates**
    - KALETRA oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of KALETRA oral solution in this patient population has not been established. However, if the benefit of using KALETRA oral solution to treat HIV infection in infants immediately after birth outweighs the potential risks, infants should be monitored closely for increases in serum osmolality and serum creatinine, and for toxicity related to KALETRA oral solution including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis. Total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients *[see Dosage and Administration (2.2) and Overdosage (10)]*.

Other Information

- Drug Safety Communication (DSC)
  - Posted on FDA website 3/8/11
- Dear Healthcare Provider Letter
  - Sent by Abbott
- Poster at Conference on Retroviruses and Opportunistic Infections (CROI) Meeting, March 2011

Questions ?